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(54) Phosphinoxide vitamin d precursors

Phosphinoxid-Vitamin D Vorläufer

Phosphinoxide-précurseurs de la vitamine D

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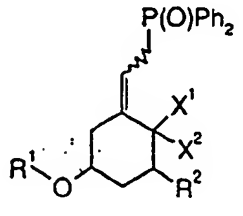
- BAGGIOLINI E G ET AL: "Stereocontrolled Total Synthesis of 1alpha,25-Dihydroxycholecalciferol1 and 1alpha,25-Dihydroxyergocalciferol" J. ORG. CHEM., vol. 51, 1986, pages 3098-3108, XP002901371

EP 1 050 537 B1

Description

[0001] The subject invention provides a process for producing a phosphine oxide of formula 1



1

where

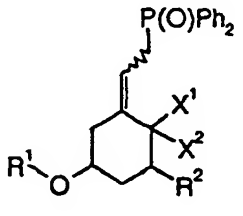
Ph	is phenyl,
X^1 and X^2	are both hydrogen or
X^1 and X^2	taken together are CH_2,
R^1	is a protecting group,
R^2	is fluorine, hydrogen, or OR^3, where R^3 is a protecting group, and the squiggly line represents a bond that results in the adjacent double bond being in either the E or Z configuration,

which can be used in the efficient synthesis of vitamin D analogues.

[0002] Vitamin D analogs, such as 1α-fluoro-25-hydroxy-16-23E-diene-26,27-bishomo-20-epi-cholecalciferol, 1,25-dihydroxy-16-ene-23-yne-26,27-bishomo-19-nor-20-epi-cholecalciferol, 1α,25-dihydroxy-18-norvitamin D3, 1α, 25-dihydroxy-18,19-dinorvitamin D3, 1α-fluoro-25-hydroxycholecalciferol, and 1α-fluoro-25-hydroxyergocalciferol, are known to have pharmaceutical activity and are useful for treating various conditions, such as psoriasis and neoplastic disease.

[0003] The key phosphine oxide compound of formula 1 ("Compound 1") below is used in the efficient synthesis of such vitamin D analogues and provides the A ring of the vitamin. Certain species of Compound 1 are known to be valuable intermediates in the synthesis of the mentioned pharmacologically active vitamin D analogues (see for example EP Publication No. 0 808 833). The remaining species of Compound 1 can be modified to be useful in the above processes or can be used for producing other vitamin D analogues, in that the compound of formula I is reacted under standard Wittig conditions with the appropriate ketone. Known processes for making this intermediate of Compound 1 typically result in low yields.

[0004] However, the subject invention provides a process to produce the desired compound of the formula 1

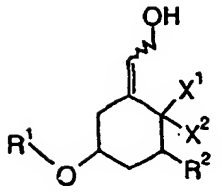


1

where

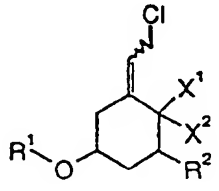
Ph	is phenyl,
X^1 and X^2	are both hydrogen or
X^1 and X^2	taken together are CH_2,
R^1	is a protecting group,
R^2	is fluorine, hydrogen, or OR^3, where R^3 is a protecting group, and the squiggly line represents a bond that results in the adjacent double bond being in either the E or Z configuration.

[0005] This process comprises chlorinating a compound of the formula 2 ("Compound 2")



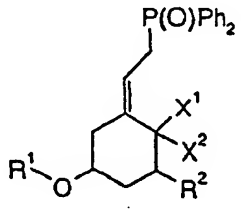
2

where X^1, X^2, R^1, R^2, and the squiggly line are as above,
using triphosgene as the chlorine source in the presence of an organic base to obtain the compound of formula 3 ("Compound 3"):

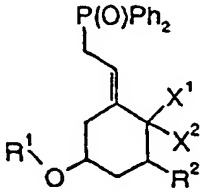


3

where X^1, X^2, R^1, R^2, and the squiggly line are as above.
The chlorine in Compound 3 is replaced by phosphine oxide a salt of diphenyl phosphine oxide that can be formed *in situ*, to obtain the compound of formula 1.
For clarity, the squiggly line is shorthand for the following two configurations:



and

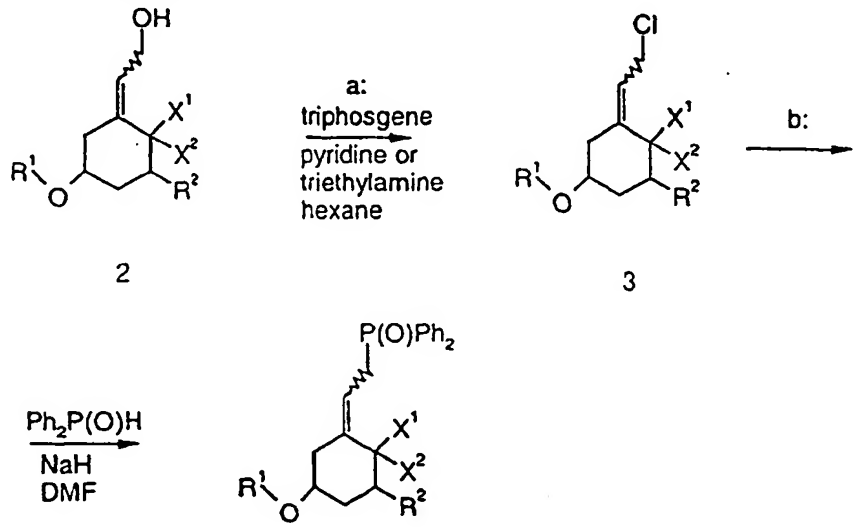


[0006] Since Compound 1 can be used in numerous synthetic pathways for producing vitamin D analogs, the bonds between the ring carbons and the OR^1 substituent and R^2 can be in either the α or β configuration as needed for the final synthesis.
Many species of Compound 2 are known. See for example, Perlman et al., *Novel synthesis of 19-nor-vitamin D compounds, Tetrahedron Lett.*, 32(52): 7663-6 (1991), Courtney et al., *Asymmetric synthesis of a key ring A synthon for 1α-hydroxy-19-nor vitamin D, Tetrahedron Lett.*, 39(21): 3363-3366 (1998), Shiuey et al. *Total synthesis of 1α-fluoro-25-hydroxycholecalciferol and -ergocalciferol., J. Org. Chem.* 55(1): 243-7 (1990), Reddy, *Synthesis and activity of 3-epi vitamin D3 compounds for use in treatment of disorders involving aberrant activity of hyperproliferative skin, parathyroid, and bone cells.*, PCT Publication No. WO 9851663, Sotojima, *Preparation of cyclohexylideneethanol derivatives as intermediates for 1α-hydroxy-and 1α,25-dihydroxyvitamin D3,* JP Kokai No. 05279283, Baggiolini et al., *Stereoselective total synthesis of 1α,25-dihydroxycholecalciferol., J. Am. Chem. Soc.*, 104(10): 2945-8 (1982). The remaining species of Compound 2 can be produced from these known compounds using procedures known in the art. Such production is well within the skill of the artisan.
In any of the above processes of this invention, R^1 can be any appropriate protecting group. The choice of an appropriate protecting group is within the skill of the artisan. By hydroxy protecting group is meant any standard compound for protecting a hydroxy group during a chemical reaction (such that the hydroxy group is easily reinstated), specifically during acidic or basic hydrolysis. However, a silyl protecting group, such as tert-butyl dimethyl silyl ("TBS") is preferred.
[0007] R^2 can be fluorine, hydrogen, or a protected hydroxy group OR^3. A protected hydroxy group is a group in which oxygen binds to the ring and is protected by a protecting group. As above, the choice of an appropriate protecting group is within the skill of the artisan. Preferred protected hydroxy groups include silyl protected hydroxy groups, such as hydroxy protected by TBS. The use of a TBS protected hydroxy group results in R^2 being *tert*-butyl dimethyl silyl oxide ("TBSO"). For any compound of this invention, R^1 and R^3 may be the same or different hydroxy protecting groups.
[0008] The salts of diphenyl phosphine oxide that can be used in the inventive process include the sodium, lithium,

and potassium salts. However, the sodium salt is preferred. In a preferred process, R^1 is TBS and R^2 is fluorine or TBSO. For the chlorination of Compound 2, a preferred amount of triphosgene is about one-half (1/2) mole relative to one (1) mole of Compound 2. Either pyridine or triethylamine may be added to the reaction. For either one, the preferred amount is 2 equivalents.

[0009] In preferred processes of this invention, R^1 is TBS, R^2 is OR^3 and R^3 is TBS. In other preferred processes, R^1 is TBS and R^2 is fluorine. In yet other preferred processes, R^1 is TBS and R^2 is hydrogen. In the subject invention, Compounds 1, 2, and 3 can have the $P(O)(Ph)_2$, OH, and Cl, respectively, in either the cis or trans position. In any of these compounds, R^1 and R^2 may be present above (▸)or below (▨) the plane of the cyclohexane ring to which they are attached. Both may be above, both may be below, or one may be above and the other may be below.

Reaction Scheme:



2 3

[0010] Compound 3 is obtained from Compound 2 by chlorinating the allylic alcohol of Compound 2 to the allylic chloride in Compound 3. This chlorinating is performed in an organic solvent, preferably an aprotic solvent such as hexane. For each mole of Compound 2, one-half (1/2) mole or more of triphosgene is used as the chlorine source. At least 2 equivalents of an organic base, preferably an aprotic amine base such as pyridine, or preferably triethylamine, should be included. Temperature is not critical and may range between -30°C and 50°C. However, a temperature around 0°C is preferred.

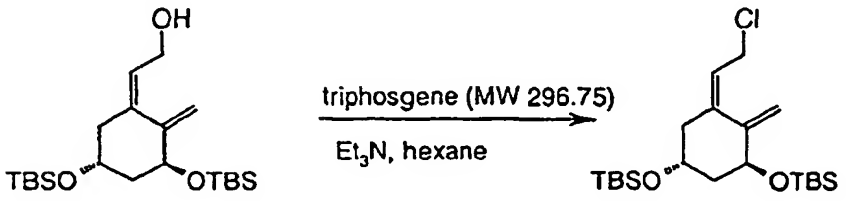
[0011] Compound 1 is obtained from Compound 3 by replacing the chlorine with phosphine oxide. Results are obtained by using an alkali metal salt of diphenylphosphine oxide, preferably the sodium salt. Other acceptable alkali metal salts include lithium and potassium salts. Such alkali metal salts of diphenylphosphine oxide are preferably generated *in situ* by reacting diphenylphosphine oxide with an alkali metal hydride. Excess reagent should be avoided to limit formation of by-products.

[0012] The Examples that follow are intended to further illustrate the invention without limiting it in any way.

Examples

Example 1 -- Preparation of (Z)-(1S,5R)-1,5-bis-(*tert*-butyl-dimethyl-silanyloxy)-3-(2-chloro-ethylidene)-2-methylene-cyclohexane

[0013]



$C_{21}H_{42}O_3Si_2$
MW 398.73

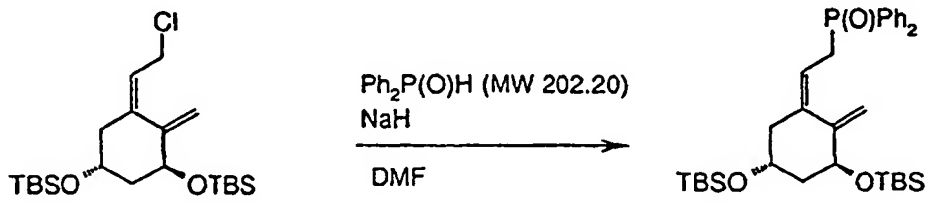
$C_{21}H_{42}ClO_2Si_2$
MW 417.17

[0014] A 500 mL, three-necked, round-bottomed flask equipped with a thermometer, mechanical stirrer, dropping funnel and nitrogen bubbler was charged with

18.2 g (45.6 mmol) of the precursor and
250 mL of hexane. To the resulting solution was added
6.76 g of triphosgene (22.8 mmol.) in one portion. The mixture was cooled with an ice-water bath, and, after a clear solution resulted,
22.3 mL (160 mmol) of triethylamine was added dropwise over 10 min with vigorous stirring. After stirring at 5 °C for 20 min, the cooling bath was removed and the resulting thick suspension was stirred at room temperature for 1 h. TLC analysis indicated complete reaction. The reaction mixture was diluted with
150 mL of hexane and washed with 2 x 250 mL =
500 mL of ice-cold 0.25*N* hydrochloric acid and 2 x 250 mL =
500 mL of water. The combined aqueous layers were back-extracted with 2 x 100 mL =
200 mL of hexane. All the organic layers were combined, washed with
150 mL of saturated sodium chloride solution, dried over magnesium sulfate and concentrated to dryness at 30 °C under reduced pressure. The residual mixture was then purged with nitrogen for 15 min to give 19.2 g of (Z)-(1S,5R)-1,5-bis-(*tert*-butyl-dimethyl-silanyloxy)-3-(2-chloro-ethylidene)-2-methylenecyclohexane as a slightly hazy, yellow oil. This material solidified upon storing overnight in a freezer and was directly used to the next step without further purification.
In-process controls: NMR ($CDCl_3$) and TLC (9:1 hexane:ethyl acetate; short-wave UV detection and PMA stain; R_f precursor = 0.2 and R_f final product = 0.6)

Example 2 -- Preparation of 3S-(3α,5β,Z)-2-2-2-methylene-bis(1,1-dimethylethyl)dimethyl-silyl-oxy-cyclohexylidene-ethyl-diphenyl phosphine oxide

[0015]



$C_{21}H_{42}ClO_2Si_2$
MW 417.17

$C_{33}H_{51}O_3PSi_2$
MW 582.90

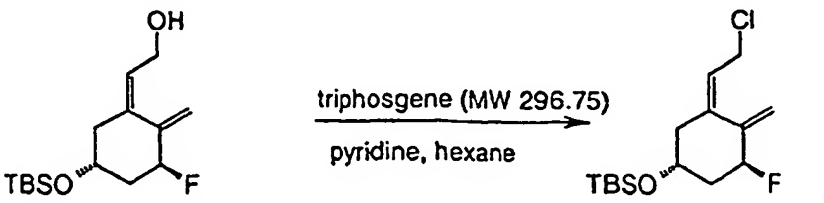
[0016] A 500 mL, three-necked, round-bottomed flask equipped with a thermometer, magnetic stirrer, dropping funnel and nitrogen bubbler was charged with

2.02 g (50.6 mmol) of sodium hydride (60% dispersion in mineral oil) and
170 mL of DMF. Then,
10.2 g (50.6 mmol) of diphenylphosphine oxide was added in one portion. Gas evolution was observed and a mild exotherm ensued that raised the temperature of the mixture to 28 °C. The mixture was stirred at room temperature for 50 min to give a slightly cloudy, yellow solution. After cooling the solution to -45 °C with a dry-ice acetone bath, a solution of
19.2 g (45.2 mmol, theoretical) of precursor in
70 mL of DMF was added dropwise over 25 min, while maintaining the reaction temperature below -35 °C. The funnel was rinsed with
10 mL of DMF and the rinse was added to the mixture. The reaction mixture was stirred at -30 to -35 °C for 1.5 h, then allowed to warm to 0 °C and stirred at that temperature for 30 min. TLC analysis indicated complete reaction. The reaction mixture was diluted with
500 mL of diethyl ether and washed with 2 x 200 mL =
400 mL of water. The combined aqueous layers were back-extracted with 2 x 150 mL =
300 mL of diethyl ether and these back-extracts were combined and washed with 2 x 200 mL =
400 mL of water. All the organic layers were combined, dried over magnesium sulfate and concentrated to dryness at 35 °C under reduced pressure. The resulting residue was further dried under high vacuum to give 26.2 g of a cloudy, yellow oil. This material was dissolved in
50 mL of hexane and the resulting solution was filtered though
150 g of TLC silica gel. The silica gel plug was then washed with
200 mL of hexane,
1 L of 9:1 hexane:ethyl acetate,
1 L of 8:2 hexane:ethyl acetate and
1 L of 7:3 hexane:ethyl acetate. The appropriate fractions were combined and concentrated to dryness at 35 °C under reduced pressure, then dried under high vacuum overnight to give 22.3 g (83.7% over two steps) of final product as a colorless foam.

In-process controls: NMR ($CDCl_3$) and TLCs (9:1 hexane:ethyl acetate; short-wave UV detection and PMA stain; R_f precursor = 0.6, 1:1 hexane:ethyl acetate; short-wave UV detection and PMA stain; R_f precursor = 0.95 and R_f final product = 0.45) _

Example 3 -- Preparation of [[(1R,3Z,5S)-3-(2-chloroethylidine)-5-fluoro-4-methylenecyclohexyl]oxy] (1,1-dimethylethyl)dimethyl silane

[0017]



$C_{15}H_{27}FO_2Si$
MW 286.46

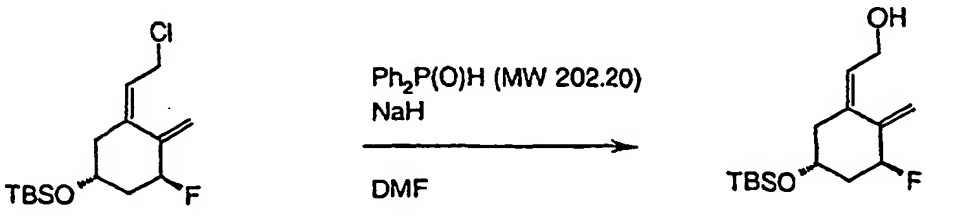
$C_{15}H_{26}ClFOSi$
MW 304.91

[0018] A 500 mL, three-necked, round-bottomed flask equipped with a thermometer, magnetic stirrer, dropping funnel with nitrogen inlet tube and outlet bubbler was charged with

8.07 g	(28.2 mmol) of precursor,
150 mL	of hexane and
4.18 g	(14.1 mmol) of triphosgene. The solution was cooled to 0 °C with an ice-acetone bath and a solution of
4.50 mL	(55.6 mmol) of pyridine in
20 mL	of hexane was added over 30 min. After stirring at 0 °C for 30 min, the cooling bath was removed and the resulting pale-yellow reaction mixture was stirred at room temperature for 30 min. Then, the reaction mixture was diluted with
250 mL	of hexane, washed with 3x200 mL =
600 mL	of saturated copper (II) sulfate solution. The combined aqueous layers were extracted with 2x100 mL =
200 mL	of hexane. The organic layers were combined, dried over magnesium sulfate and concentrated to dryness on a rotary evaporator to give 9.0 g (overweight) of final product as a pale yellow oil
	In-process controls: NMR ($CDCl_3$) and TLC (4:1 hexane:ethyl acetate; short-wave UV detection and PMA stain; R_f precursor = 0.3 and R_f final product = 0.9).

Example 4 -- Preparation of (S-trans)-1-fluoro-5-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-2-methenyl-3-[(diphenylphosphinyl)ethylidene]-cyclohexane

[0019]



$C_{15}H_{26}ClFOSi$
MW 304.91

$C_{27}H_{35}FO_2PSi$
MW 470.64

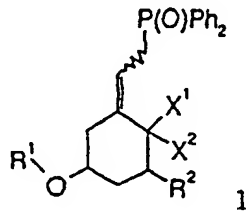
[0020] A 100 mL, three-necked, round-bottomed flask equipped with a thermometer, magnetic stirrer, dropping funnel with nitrogen inlet tube and outlet bubbler was charged with

50 mL	of DMF and
1.33 g	(33.1 mmol) of sodium hydride (60% dispersion in mineral oil). While cooling with a water bath (10 °C),

6.70 g (33.1 mmol) of diphenylphosphine oxide was added in small portions over 15 min. The water bath was removed and the resulting yellow solution was stirred at room temperature for 30 min. After cooling to -60 °C with a dry-ice acetone bath, a solution of
9.0 g (28.2 mmol, in theory) of precursor in
20 mL DMF was added dropwise, via a syringe, over 15 min, while maintaining the temperature of the reaction mixture below -50 °C. The reaction mixture was stirred at -60 °C for 2 h, then allowed to warm to room temperature over 1 h. The reaction mixture was diluted with
600 mL of diethyl ether and washed with 3x200 mL =
600 mL of water. The combined aqueous layers were extracted with
200 mL of diethyl ether. The organic layers were combined, dried over magnesium sulfate and concentrated under reduced pressure to give a white solid. This crude product was recrystallized from
25 mL of diisopropyl ether. The resulting solid was collected by filtration, washed with
5 mL of cold diisopropyl ether and dried under high vacuum to give 7.93 g (59.8%) of final product as a white solid. The mother liquor was concentrated and the residue was subjected to chromatography on silica gel, eluting with 7:3-1:1 hexane:ethyl acetate. The appropriate fractions were combined and concentrated to dryness to give 2.22 g (16.7%) of final product. Thus, the total yield of final product was 10.1 g (76.5% overall from precursor).
In-process controls: NMR ($CDCl_3$) and TLC (1:1 hexane:ethyl acetate; short-wave UV detection and PMA stain; R_f precursor = 1.0 and R_f final product = 0.28).

Claims

1. A process for producing a compound of the formula:



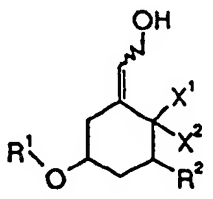
1

where

Ph is phenyl,
X^1 and X^2 are both hydrogen or
X^1 and X^2 taken together are CH_2,
R^1 is a protecting group,
R^2 is fluorine, hydrogen, or OR^3, where R^3 is a protecting group,
and the squiggly line represents a bond that results in the adjacent double bond being in either the E or Z configuration,

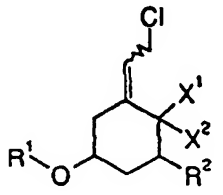
which comprises:

(a) chlorinating a compound of the formula:



2

where X^1, X^2, R^1, R^2, and the squiggly line are as above,
using triphosgene in the presence of an organic base to obtain the compound of the formula:



3

where X^1, X^2, R^1, R^2, and the squiggly line are as above;
and
(b) reacting the compound of formula 3 with a salt of diphenyl phosphine oxide to obtain the compound of formula 1.

2. The process of claim 1, wherein R^1 is a silyl protecting group.

3. The process of claim 2, wherein R^1 is a *tert*-butyl dimethyl silyl group.

4. The process of claim 1 or 2, wherein R^2 is fluorine or OR^3 and R^3 is *tert*-butyl dimethyl silyl

5. The process of anyone of claims 1 to 4, wherein X^1 and X^2 taken together are CH_2.

6. The process of claim 1, wherein the chlorinating of step (a) is performed using triphosgene in the presence of an organic base which is pyridine or triethylamine.

7. The process of claim 1, wherein the chlorinating of step (a) is performed in an organic solvent.

8. The process of claim 1, wherein the chlorinating of step (a) is performed at a temperature of from -30°C to 50°C, preferably at a temperature of about 0°C.

9. The process of claim 1, wherein the reacting of step (b) is performed using a salt of diphenyl phosphine oxide that has been generated *in situ* by reacting diphenyl phosphine oxide with a alkali metal hydride.

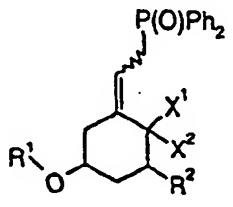
10. The process of claim 1, wherein the reacting of step (b) is performed using the sodium salt of diphenyl phosphine oxide.

11. The process of claim 1, wherein the reacting of step (b) is performed using the sodium salt of diphenyl phosphine oxide that has been generated *in situ* by reacting diphenyl phosphine oxide with sodium hydride.

12. The process of claim 1, wherein the reacting of step (b) is performed in an organic solvent.

13. The process of claim 1, wherein the reacting of step (b) is performed at a temperature of from -80°C to 50°C, preferably at a temperature of about -60°C.

14. A process for producing a compound of the formula:



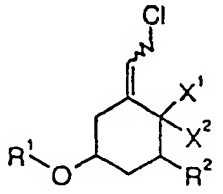
1

where

Ph	is phenyl,
X^1 and X^2	are both hydrogen or
X^1 and X^2	taken together are CH_2,
R^1	is a protecting group,
R^2	is fluorine, hydrogen, or OR^3, where R^3 is a protecting group, and the squiggly line represents a bond that results in the adjacent double bond being in either the E or Z configuration,

which comprises:

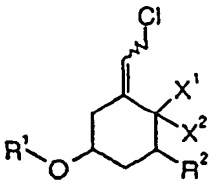
reacting a compound of the formula:



3,

where X^1, X^2, R^1, R^2, and the squiggly line are as above with a salt of diphenyl phosphine oxide to obtain the compound of formula 1.

15. A process for producing a compound of the formula:



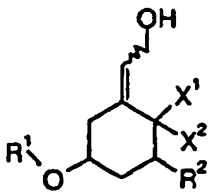
3,

where

X^1 and X^2	are both hydrogen or
X^1 and X^2	taken together are CH_2,
R^1	is a protecting group,
R^2	is fluorine, hydrogen, or OR^3, where R^3 is a protecting group, and the squiggly line represents a bond that results in the adjacent double bond being in either the E or Z configuration,

which comprises:

chlorinating a compound of the formula:

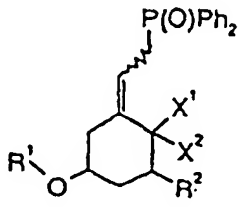


2

where X^1, X^2, R^1, R^2, and the squiggly line are as above, using triphosgene in the presence of an organic base to obtain the compound of formula 3.

Patentansprüche

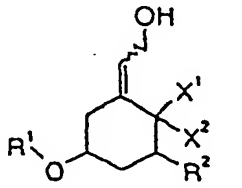
1. Verfahren zur Herstellung einer Verbindung der Formel



1

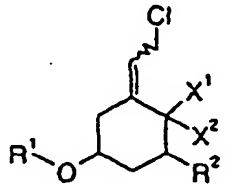
worin
Ph Phenyl ist
X^1 und X^2 beide Wasserstoff sind oder
X^1 und X^2 zusammen CH_2 sind,
R^1 eine Schutzgruppe ist,
R^2 Fluor, Wasserstoff oder OR^3 ist, wobei R^3 eine Schutzgruppe ist, und die Zickzacklinie eine Bindung bedeutet, die dazu führt, dass die benachbarte Doppelbindung entweder in E- oder Z-Konfiguration ist,
das umfasst:

(a) Chlorieren einer Verbindung der Formel



2

worin X^1, X^2, R^1, R^2 und die Zickzacklinie wie oben definiert sind,
unter Verwendung von Triphosgen in Gegenwart einer organischen Base, um die Verbindung der Formel



3

zu erhalten, worin X^1, X^2, R^1, R^2 und die Zickzacklinie wie oben definiert sind und
(b) Umsetzen der Verbindung der Formel 3 mit einem Salz von Diphenylphosphinoxid, um die Verbindung der Formel 1 zu erhalten.

2. Verfahren nach Anspruch 1, wobei R^1 eine Silylschutzgruppe ist.

3. Verfahren nach Anspruch 2, wobei R^1 eine tert.-Butyldimethylsilylgruppe ist.

4. Verfahren nach Anspruch 1 oder Anspruch 2, wobei R^2 Fluor oder OR^3 ist und R^3 tert.-Butyldimethylsilyl ist.

5. Verfahren nach einem der Ansprüche 1 bis 4, wobei X^1 und X^2 zusammen CH_2 sind.

6. Verfahren nach Anspruch 1, wobei die Chlorierung von Stufe (a) durchgeführt wird unter Verwendung von Triphosgen in Gegenwart einer organischen Base, die Pyridin oder Triethylamin ist.

7. Verfahren nach Anspruch 1, wobei die Chlorierung von Stufe (a) in einem organischen Lösungsmittel durchgeführt wird.

8. Verfahren nach Anspruch 1, wobei die Chlorierung von Stufe (a) bei einer Temperatur von -30°C bis 50°C, bevorzugt bei einer Temperatur von etwa 0°C durchgeführt wird.

9. Verfahren nach Anspruch 1, wobei die Reaktion von Stufe (b) unter Verwendung eines Salzes von Diphenylphosphinoxid durchgeführt wird, das in situ erzeugt wurde, indem Diphenylphosphinoxid mit einem Alkalihydrid umgesetzt wurde.

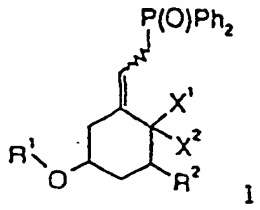
10. Verfahren nach Anspruch 1, wobei die Reaktion von Stufe (b) durchgeführt wird unter Verwendung des Natriumsalzes von Diphenylphosphinoxid.

11. Verfahren nach Anspruch 1, wobei die Reaktion von Stufe (b) durchgeführt wird unter Verwendung des Natriumsalzes von Diphenylphosphinoxid, das in situ erzeugt wurde, indem Diphenylphosphinoxid mit Natriumhydrid umgesetzt wurde.

12. Verfahren nach Anspruch 1, wobei die Reaktion von Stufe (b) in einem organischen Lösungsmittel durchgeführt wird.

13. Verfahren nach Anspruch 1, wobei die Reaktion von Stufe (b) bei einer Temperatur von -80°C bis 50°C, bevorzugt bei einer Temperatur von etwa -60°C durchgeführt wird.

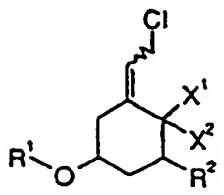
14. Verfahren zur Herstellung einer Verbindung der Formel



I

worin
Ph Phenyl ist
X^1 und X^2 beide Wasserstoff sind oder
X^1 und X^2 zusammen CH_2 sind,
R^1 eine Schutzgruppe ist,
R^2 Fluor, Wasserstoff oder OR^3 ist, wobei R^3 eine Schutzgruppe ist, und die Zickzacklinie eine Bindung bedeutet, die dazu führt, dass die benachbarte Doppelbindung entweder in E- oder Z-Konfiguration ist,
das umfasst:

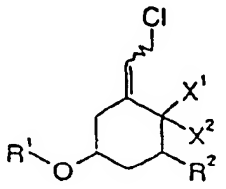
dass eine Verbindung der Formel



3

worin X^1, X^2, R^1, R^2 und die Zickzacklinie wie oben definiert sind, mit einem Salz von Diphenylphosphinoxid umgesetzt wird, um die Verbindung der Formel 1 zu erhalten.

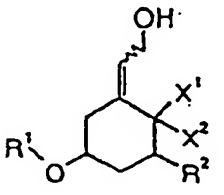
15. Verfahren zur Herstellung einer Verbindung der Formel



3

worin
X^1 und X^2 beide Wasserstoff sind oder
X^1 und X^2 zusammen CH_2 bilden,
R^1 eine Schutzgruppe ist,
R^2 Fluor, Wasserstoff oder OR^3 ist, wobei R^3 eine Schutzgruppe ist, und die Zickzacklinie eine Bindung bedeutet, die dazu führt, dass die benachbarte Doppelbindung entweder in E- oder Z-Konfiguration ist, das umfasst:

dass eine Verbindung der Formel



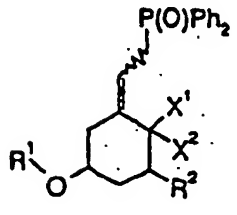
2

chloriert wird, wobei X^1, X^2, R^1, R^2 und die Zickzacklinie wie vorher definiert sind,

unter Verwendung von Triphosgen in Gegenwart einer organischen Base, um die Verbindung der Formel 3 zu erhalten.

Revendications

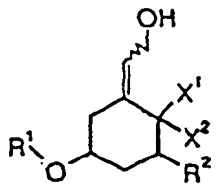
1. Procédé de production d'un composé de formule



1

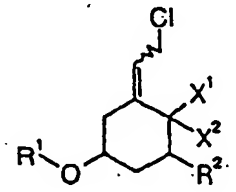
où
Ph est phényle,
X^1 et X^2 sont l'un et l'autre l'hydrogène ou
X^1 et X^2 combinés sont CH_2,
R^1 est un groupe protecteur,
R^2 est le fluor, l'hydrogène ou OR^3 où R^3 est un groupe protecteur,
et le trait sinueux représente une liaison telle que la double liaison adjacente est dans la configuration E ou Z, qui comprend :

(a) la chloration d'un composé de formule :



2

où X^1, X^2, R^1, R^2 et le trait sinueux sont comme ci-dessus,
avec le triphosgène en présence d'une base organique pour obtenir le composé de formule :



3

où X^1, X^2, R^1, R^2 et le trait sinueux sont comme ci-dessus ;
et
(b) la réaction du composé de formule 3 avec un sel d'oxyde de diphénylphosphine pour obtenir le composé de formule 1.

2. Procédé selon la revendication 1 où R^1 est un groupe protecteur silyle.

3. Procédé selon la revendication 2 où R^1 est un groupe protecteur tert-butyldiméthylsilyle.

4. Procédé selon la revendication 1 ou 2 où R^2 est le fluor ou OR^3 et R^3 est tert-butyldiméthylsilyle.

5. Procédé selon l'une quelconque des revendications 1 à 4 où X^1 et X^2 combinés sont CH_2.

6. Procédé selon la revendication 1 où la chloration de l'étape (a) est conduite avec le triphosgène en présence d'une base organique qui est la pyridine ou la triéthylamine.

7. Procédé selon la revendication 1 où la chloration de l'étape (a) est conduite dans un solvant organique.

8. Procédé selon la revendication 1 où la chloration de l'étape (a) est conduite à une température de -30°C à 50°C, de préférence à une température d'environ 0°C.

9. Procédé selon la revendication 1 où la réaction de l'étape (b) est conduite avec un sel d'oxyde de diphénylphosphine qui a été formé in situ par réaction de l'oxyde de diphénylphosphine avec un hydrure de métal alcalin.

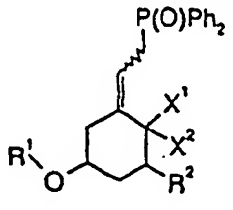
10. Procédé selon la revendication 1 où la réaction de l'étape (b) est conduite avec le sel de sodium de l'oxyde de diphénylphosphine.

11. Procédé selon la revendication 1 où la réaction de l'étape (b) est conduite avec le sel de sodium de l'oxyde de diphénylphosphine qui a été formé in situ par réaction de l'oxyde de diphénylphosphine avec l'hydrure de sodium.

12. Procédé selon la revendication 1 où la réaction de l'étape (b) est conduite dans un solvant organique.

13. Procédé selon la revendication 1 où la réaction de l'étape (b) est conduite à une température de -80°C à 50°C, de préférence à une température d'environ -60°C.

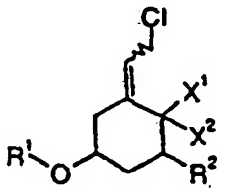
14. Procédé de production d'un composé de formule



1

où
Ph est phényle,
X^1 et X^2 sont l'un et l'autre l'hydrogène ou
X^1 et X^2 combinés sont CH_2,
R^1 est un groupe protecteur,
R^2 est le fluor, l'hydrogène ou OR^3 où R^3 est un groupe protecteur,
et le trait sinueux représente une liaison telle que la double liaison adjacente est dans la configuration E ou Z,
qui comprend :

la réaction d'un composé de formule :

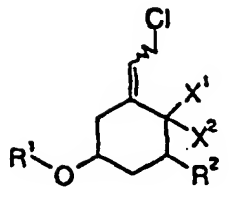


3

où X^1, X^2, R^1, R^2 et le trait sinueux sont comme ci-dessus,

avec un sel d'oxyde de diphénylphosphine pour obtenir le composé de formule 1.

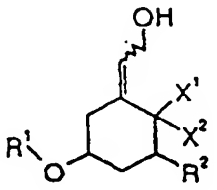
15. Procédé de production d'un composé de formule



3

où
X^1 et X^2 sont l'un et l'autre l'hydrogène ou
X^1 et X^2 combinés sont CH_2,
R^1 est un groupe protecteur,
R^2 est le fluor, l'hydrogène ou OR^3 où R^3 est un groupe protecteur,
et le trait sinueux représente une liaison telle que la double liaison adjacente est dans la configuration E ou Z,
qui comprend :

la chloration d'un composé de formule :



2

où X^1, X^2, R^1, R^2 et le trait sinueux sont comme ci-dessus,
avec le triphosgène en présence d'une base organique pour obtenir le composé de formule 3.